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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,514	03/29/2002	Koji Yanai	2002_0451A	7814

7590 10/18/2005

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,514	YANAI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,17,19-21,23 and 25-37* is/are pending in the application.

4a) Of the above claim(s) *23 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,17,19-21 and 26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 5-7, 17, 19-21, 23 and 25-37 are pending.

Applicants' amendment filed July 26, 2005 is acknowledged. Applicants' response has been fully considered. Claims 1, 5-7, 17, 19-21, 23, 25, 26, 28 and 30 have been amended, claims 2-4, 8-16, 18, 22 and 24 have been cancelled, and new claims 32-37 have been added. Upon consideration, nucleotide sequences SEQ ID NO: 3 and 5, and nucleotides encoding amino acid sequences SEQ ID NO:2, 4 and 6 will be included for examination. Claims 23 and 25 are non-elected inventions and withdrawn from consideration. Therefore, claims 1, 5-7, 17, 19-21, and 26-37 are examined.

Withdrawn-Objections to the Specification

2. The previous objection to the specification is withdrawn in view of applicant's submission of a new abstract, applicant's amendment to the specification, and applicant's response at page 14 in the amendment filed July 26, 2005.

Withdrawn-Claim Objections

3. The previous objection to claims 6 and 10-22 is withdrawn in view of applicant's cancellation of the claim, applicant's amendment to the claim, and applicant's response at page 14 in the amendment filed July 26, 2005.

Withdrawn Claim Rejections - 35 USC § 112

4. The previous rejection of claims 8-16, 18 and 22, under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed July 26, 2005.

5. The previous rejection of claims 20 and 21, under 35 U.S.C. 112, first paragraph, regarding the deposited material, is withdrawn in view of applicants' deposit receipts submitted with the filing of the application, and applicant's response in the amendment filed July 26, 2005.

6. The previous rejection of claims 1-20 and 22, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' cancellation of the claim, applicant's amendment to the claim, and applicant's response at pages 14-15 in the amendment filed July 26, 2005.

Withdrawn Claim Rejections - 35 USC § 101

7. The previous rejection of claims 26-27, under 35 U.S.C. 101, is withdrawn in view of applicants' amendment to the claim in the amendment filed July 26, 2005.

Withdrawn Claim Rejections - 35 USC § 102

8. The previous rejection of claims 1-5 and 18 under 35 U.S.C. 102(b) as anticipated by Blanc *et al.* (Mol. Microbiology 23, 191-202 (1997)), is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim and applicant's response at pages 18-19 in the amendment filed July 26, 2005.

New Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 5-7, 19-21, 33 and 35-37 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 5 is indefinite because of the use of the term of "at least one amino acid selected from .....and phenyllactic acid". The term cited renders the claim indefinite, it is not clear how phenyllactic acid can be an amino acid since it does not contain an amino group.

11. Claims 1, 5-7, 19-21, 33 and 35-37 are indefinite because of the use of the term "one to several modifications". The term cited renders the claim indefinite, it is not clear how many modifications are intended for the modified sequences, e.g., is it 5, 10, 20, 50 or 100? Claims 5-7, 19-21 and 35-37 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

Maintained Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. ɔ 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Previous rejection of claims 1, 5-7, 19-21 and 26 under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is maintained, and claims 28, 30, 32, 33 and 35-37 are added. The response to applicants' argument is indicated below. The instant claims are drawn to transformants comprising a polynucleotide (or the polynucleotide itself), wherein the polynucleotide sequence encodes SEQ ID NO:2 or a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, the polynucleotide sequence encodes SEQ ID NO:4 or SEQ ID NO:4 having 4-amino-4-

deoxychorismic acid mutase activity, and/or, the polynucleotide sequence encodes SEQ ID NO:6 or SEQ ID NO:6 having 4-amino-4-deoxyprephenic acid dehyrogenase activity.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, genes encoding a synthase (papA), mutase (papB), and dehydrogenase (papC) of the claimed invention are described from *S. venezuelae* (SEQ ID NOs:1-6); the prior art teaches analogous genes from *S. pristinaespiralis* (see Blanc *et al.*). The instant claims are drawn to, for example (claim 1), a polynucleotide encoding "the amino acid sequence of SEQ ID NO:2 or a **modified** sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity" wherein said modification is defined as one or more (e.g., one to several) substitutions, deletions, insertions, or additions (see page 13), which definition is essentially limitless on the amount of modification to the named structure of SEQ ID NO:2.

Since the enzyme does not garner a particular structural feature as based on the art, the enzyme name cannot support both a structural and functional limitation for the product of the claimed invention. Furthermore, there is no disclosure of any particular structure to function/activity relationship in the disclosed enzymes. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. The lack of a structure to function/activity relationship in the disclosed enzymes and the lack of representative species for the polynucleotides encoding the enzyme variants as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicants indicate independent claim 1 has been amended in product-by-process format and incorporates the limitations of claims 4, 16, 18 and 24. In other words, the claims have been amended to recite specific steps for transforming the microorganism to produce the transformant, including the specific sequences, i.e., SEQ ID NOS: 1-6, utilized in the process. Furthermore, the number of modifications is limited to "one to several" and the type of modifications have been defined as "a substitution, a deletion, an insertion, and an addition"; and the functional activity of the enzyme has been included as a positive limitation for the modified sequences as suggested by the Examiner during the interview. In sum, the amended claims are drawn to the specific embodiments, i.e., SEQ ID NOS: 1-6 and the chemical formulae for PF 1022 and the derivative thereof as exemplified in the disclosure. Therefore, written description for the amended claims is satisfied by disclosure (pages 15-17 of the response).

Applicants' response has been considered, however, the argument is not persuasive regarding the polynucleotides encoding the modified sequence of SEQ ID NO:2, 4 or 6 having the desired enzyme activity because there is no disclosure of any particular structure to function/activity relationship for the disclosed enzymes, and lack of representative species in the specification, one of skill in the art would be unable to identify the structure of a modified enzyme that has desired activity. Although the number of modification and types of modification have been limited somewhat for the modified sequences, there are still unspecified variants encompassed by the claimed invention. Therefore, as indicated above, applicants have failed to sufficiently describe the claimed invention.

13. Previous rejection of claims 1, 5-7, 17 and 19-21 under 35 U.S.C. § 112, first paragraph,, scope of enablement, is maintained, and claims 32, 33 and 35-37 are added, because the specification, while being enabling for transformants of *Mycelia sterilia* containing genes encoding SEQ ID NOs: 2, 4, and 6 that make para-substituted PF1022 wherein the substitution is a $-NO_2$ or $-NH_2$ functional group, does not reasonably provide enablement for any transformant to make a peptide or depsipeptide having a benzene ring substituted at para-position with a nitro or amino group using a gene encoding a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, a modified sequence of SEQ ID NO:4 having 4-amino-4-deoxychorismic acid mutase activity, and/or, SEQ ID NO:6 having 4-amino-4-deoxyprephenic acid dehyrogenase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make the claims to the full extent of their scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification teaches the identification of papA, papB, and papC genes in *Streptomyces venezuelae* as found in the vicinity of the known gene pabAB. The pabAB encodes p-aminobenzoic acid synthase; the papA, papB, and papC genes are described as encoding a synthase, a mutase, and a dehydrogenase, respectively (see both Blanc *et al.* and the instant specification) and such activities are distinct from that of pabAB. The papA, papB, and papC genes are described as being analogous to papA, papB, and papC genes from *S. pristinaespiralis*, which microorganism naturally produces pristinamycin - a secondary peptide

metabolite containing a benzene ring with a para-substituted group that is a nitrogen-containing group (see Blanc *et al.*).

The instant inventors use the papA, papB, and papC genes in a fungus that produces PF1022 (called *Mycelia sterilia* and *Rosellinia sp.* PF1022 in the art) to produce -NO_2 and -NH_2 -para-substituted PF1022 analogs (see Figure 13). These analogs are produced due to the incorporation of the newly produced p-amino-D-phenyllactate that is incorporated into PF1022 in place of D-phenyllactate that is incorporated natively (see Yanai *et al.* 2004, Figure 2). Thus, the teachings of the instant specification enable the production of metabolite analogs wherein the native metabolite incorporates phenyllactate and wherein -NO_2 or -NH_2 analogs are produced using host cells transformed with papA, papB, and papC genes. However, due to the specificity of biosynthetic enzymes, which specificity is well know in the art, other analogs are not enabled and the use of other genes (even the identification of other genes) is not enabled. While one of skill in the art may be able to *find* other papA, papB, and papC genes using hybridization techniques and a knowledge of organisms that may produce/use p-aminophenylpyruvate (the product of the papA-papB-papC pathway), this does not enable one of skill in the art to *make* such genes for use in the claimed transformants because the relevant characteristics of these genes and/or the enzymes they encode so that their functional properties are maintained are unknown. The predictability of the ability of papA, papB, and papC enzymes to incorporate a nitro or amino group in the para position of any peptide or depsipeptide is very, very low.

Response to Arguments

Applicants indicate the claims have been amended to the specific transformants of Mycelia sterilia containing genes encoding SEQ ID NOS: 2, 4, and 6 and the specifically

disclosed metabolite, PF1022 and derivative thereof, as defined by their chemical name and formulae. In other words, the amended claims are limited to that which the Examiner indicated is enabled (pages 17-18 of the response).

Applicants' response has been considered, however, the argument is not persuasive because the independent claim 1 is not only directed to transformants of *Mycelia sterilia* containing genes encoding SEQ ID NOS: 2, 4, and 6 and the specifically disclosed metabolite, PF1022 and derivative thereof, but also to the genes encoding modified sequences of SEQ ID NO:2, 4 and 6, and to an unspecified metabolite (i.e., peptide or depsipeptide) having a benzene ring substituted at para-position with a nitro or amino group. Since the correlation of structure and function of these genes is unknown, undue experimentation is required to identify the genes encoding modified sequences of SEQ ID NO:2, 4 and 6 that have desired enzyme activity, thus the full scope of the claims is not enabled as indicated in the section above.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Previous rejection of claim 26 under 35 U.S.C. § 102(b) as being anticipated by Blanc *et al.* (Mol. Microbiology 23, 191-202 (1997)) is maintained, and claims 28 and 30 are added. The response to arguments is indicated below.

Claims 26, 28 and 30 encompass a polynucleotide encoding a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, a polynucleotide encoding a

modified sequence of SEQ ID NO:4 having 4-amino-4-deoxychorismic acid mutase activity, and a polynucleotide encoding a modified sequence of SEQ ID NO:6 having 4-amino-4-deoxyprephenic acid dehyrogenase activity, respectively.

Blanc *et al.* teach the papA gene of *Streptomyces pristinaespiralis* (nucleotides 68-2227) which encodes 4-amino-4-deoxychorismic acid synthase (see abstract and page 196, right column, Fig. 4) that has a modified sequence of SEQ ID NO:2 (see attached sequence alignment; claim 26); the papB gene of *Streptomyces pristinaespiralis* (nucleotides 3413-3802), which encodes 4-amino-4-deoxychorismic acid mutase that has a modified sequence of SEQ ID NO:4 (see attached sequence alignment; claim 28); and the papC gene of *Streptomyces pristinaespiralis* (nucleotides 2486-3376), which encodes 4-amino-4-deoxyprephenic acid dehyrogenase that has a modified sequence of SEQ ID NO:6 (see attached sequence alignment; claim 30).

Response to Arguments

Applicants indicate claim 1 has been amended to incorporate the subject matter of claims 10, 12, 14, 16 and 24, which were not included in the rejection, thus, the present amendment overcomes the rejection (pages 18 and 19 of the response).

Applicants' response has been considered, regarding claims 1-5 and 18, the argument is persuasive and the rejection is withdrawn. However, regarding claim 26, the argument is not found persuasive, since Blanc *et al.* teach a papA gene encoding a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, which is the claimed invention.

Conclusion

15. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

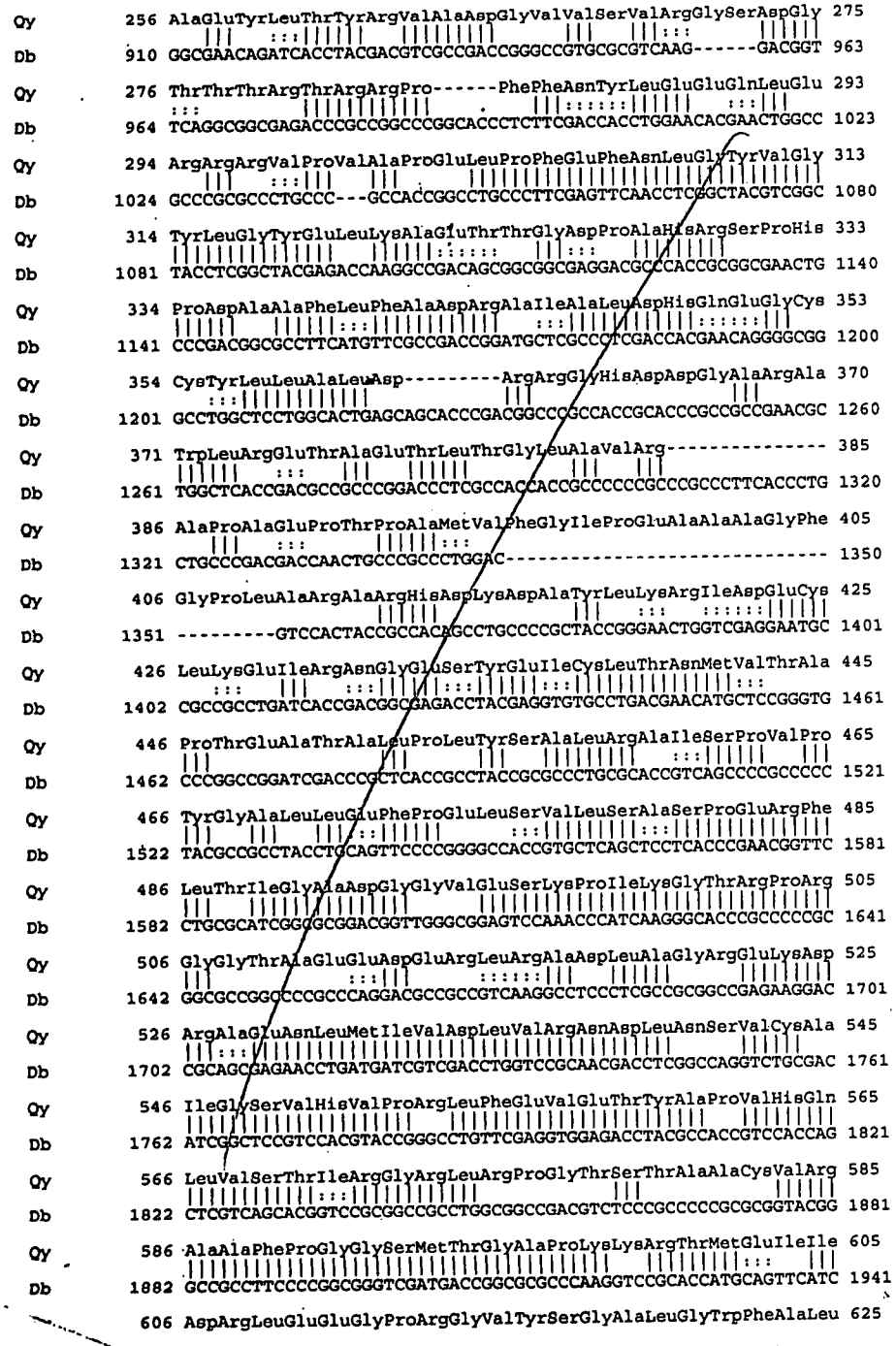
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

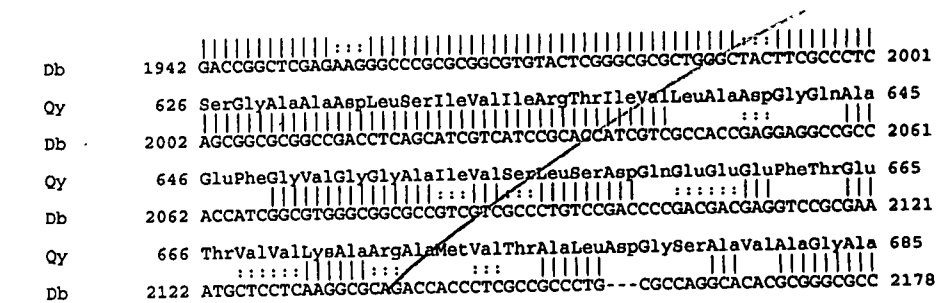
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CMK
October 10, 2005

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER





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ACCESSION U60417
VERSION U60417.1 GI:1575335
KEYWORDS .
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ORGANISM Streptomyces pristinaespiralis
Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales; Streptomycineae; Streptomycetaceae; Streptomyces.
REFERENCE 1 (bases 1 to 4740)
AUTHORS Blanc,V., Gil,P., Bamas-Jacques,N., Lorenzon,S., Zagorec,M., Schleuniger,J., Bisch,D., Blanche,F., Debussche,L., Crouzet,J. and Thibaut,D.
TITLE Identification and analysis of genes from Streptomyces pristinaespiralis encoding enzymes involved in the biosynthesis of the 4-dimethylamino-L-phenylalanine precursor of pristinamycin I
JOURNAL Mol. Microbiol. 23 (2), 191-202 (1997)
MEDLINE 97197164
PUBMED 9044253
REFERENCE 2 (bases 1 to 4740)
AUTHORS Blanc,V., Gil,P., Bamas-Jacques,N., Lorenzon,S., Schleuniger,J., Bisch,D., Blanche,F., Debussche,L., Crouzet,J. and Thibaut,D.
TITLE Direct Submission
JOURNAL Submitted (11-JUN-1996) Recherche Pharmaceutique, Rhone-Poulenc Rorer, 13 quai Jules Guesde, B. P. 14, Vitry sur Seine cedex 94403, France

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                     AGEEGLGMIRAMERTAARLLAPGGVLLLEHGSYQLASVPALFRATGRWSHASSRPTCN
                     DGCLTAVRNHTCAPPA"
ORIGIN

Alignment Scores:
Pred. No.:                5.86e-80      Length:          4740
Score:                    1816.00       Matches:         385
Percent Similarity:       64.03%        Conservative:    76
Best Local Similarity:    53.47%        Mismatches:      207
Query Match:              50.83%        Indels:          52
DB:                       1             Gaps:            11

US-10-089-514-2 (1-686) x SPU60417 (1-4740)

Qy          1 MetArgThrLeuLeuIleAspAsnTyrAspSerPheThrHisAsnLeuPheGlnTyrIle 20
              :::||||||||||||||||||||||||||||||||||||||:::|||||||||||||  :::
Db         77 GTGCGAACCCTGCTGATCGACAACTACGACTCGTTCACCTACAACCTCTTCCAGATGCTG 136

Qy         21 GlyGluAlaThrGlyGlnProProValValValProAsnAsp------AlaAspTrpSer 38
                 |||       |||      |||:::||||||   ||||||          |||
Db        137 GCCGAGGTGAACGGCGCCGCTCCGCTCGTCGTCCGCAACGACGACACCCGCACCTGGCAG 196

Qy         39 ArgLeuProValGluAspPheAspAlaIleValValSerProGlyProGlySerProAsp 58
                 |||       |||||||||   :::|||||||||||||||||||||   |||
Db        197 GCCCTGGCGCCGGGCGACTTCGACAACGTCGTCGTCTCACCCGGCCCCGGCCACCCCGCC 256

Qy         59 ArgGluArgAspPheGlyIleSerArgArgAlaIleThrAspSerGlyLeuProValLeu 78
              :::   |||   |||:::||||||||   ||||||:::       ||||||:::|||
Db        257 ACCGACACCGACCTGGGCCTCAGCCGCCGGGTGATCACCGAATGGGACCTGCCGCTGCTC 316

Qy         79 GlyValCysLeuGlyHisGlnGlyIleAlaGlnLeuPheGlyGlyThrValGlyLeuAla 98
              ||||||||||||||||||||||  :::   |||  |||      |||   |||
Db        317 GGGGTGTGCCTGGGCCACCAGGCCCTGTGCCTGCTCGCCGGCGCCGCCGTCGTCCACGCA 376

Qy         99 ProGluProMetHisGlyArgValSerGluValArgHisThrGlyGluAspValPheArg 118
              |||||||||  |||||||||  |||::::::||||||  |||:::  :::|||
Db        377 CCCGAACCCTTTCACGGCCGCACCAGCGACATCCGCCACGACGGGCAGGGCCTGTTCGCG 436

Qy        119 GlyLeuProSerProPheThrAlaValArgTyrHisSerLeuAlaAlaThrAspLeuPro 138
                :::|||||||||   |||  ||||||||||||||||||                |||||
Db        437 AACATCCCCTCCCCGCTGACCGTGGTCCGCTACCACTCGCTGACCGTCCGGCAACTGCCC 496

Qy        139 AspGluLeuGluProLeuAlaTrpSerAspAspGlyValValMetGlyLeuArgHisArg 158
                :::|||          |||  :::  ||||||  :::|||  :::  ||||||
Db        497 GCCGACCTGCGCGCCACCGCCCACACCGCCGACGGGCAGCTGATGGCCGTCGCCCACCGC 556

Qy        159 GluLysProLeuTrpGlyValGlnPheHisProGluSerIleGlySerAspPheGlyArg 178
                  |||   :::||||||||||||||||||||||||||||||  |||:::   |||
Db        557 CACCTGCCCCGCTTCGGCGTGCAGTTCCACCCCGAATCGATCAGCAGCGAACACGGCCAC 616

Qy        179 GluIleMetAlaAsnPheArgAspLeuAlaLeu------AlaHisHisArg--------- 193
                :::::|||||||||||||||||||:::|||      |||  ||||||
Db        617 CGGATGCTCGCCAACTTCCGCGACCTGTCCCTGCGCGCGGCCGGCCACCGCCCCCCGCAC 676

Qy        194 AlaArgArgHisGlyAlaAspSerPro------------------------------- 202
                  |||   |||  :::|||
Db        677 ACCGAACGCATACCCGCACCCGCACCCGCCCCCGCCCCCGCCCCCGCACCGGCACCGCCC 736

Qy        203 --------------------TyrGluLeuHisValArgArgValAspValLeuProAsp 215
                                  |||  ||||||||||||  |||      :::||||||
Db        737 GCGTCCGCGCCGGTGGGGGAGTACCGGCTGCATGTGCGCGAGGTCGCCTGCGTGCCCGAC 796

Qy        216 AlaGluGluValArgArgGlyCysLeuProGlyGluGlyThrThrPheTrpLeuAspSer 235
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Db        797 GCGGACGCCGCGTTCACCGCCCTGTTCGCCGACGCCCCGGCCCGGTTCTGGCTCGACAGC 856

Qy        236 SerSerValLeuGluGlyAlaSerArgPheSerPheLeuGlyAspAspArgGlyProLeu 255
                |||   |||   |||  :::||||||::||||||||          |||||||||
Db        857 AGCCGCGTCGAGCCGGGCCTCGCCCGCTTCACCTTCCTCGGCGCCCCCGCCGGCCCGCTC 916

Qy        256 AlaGluTyrLeuThrTyrArgValAlaAspGlyValValSerValArgGlySerAspGly 275
                |||  :::||||||  ||||||||||  |||  |||:::  ||||||
Db        917 GGCGAACAGATCACCTACGACGTCGCCGACCGGGCCGTGCGCGTCAAG------GACGGT 970

Qy        276 ThrThrThrArgThrArgArgPro------PhePheAsnTyrLeuGluGluGlnLeuGlu 293
                :::       ||||||||||||       |||::::::||||||  :::|||
Db        971 TCAGGCGGCGAGACCCGCCGGCCCGGCACCCTCTTCGACCACCTGGAACACGAACTGGCC 1030

Qy        294 ArgArgArgValProValAlaProGluLeuProPheGluPheAsnLeuGlyTyrValGly 313
                |||   :::|||  |||  ||||||||||||||||||||||||||||||||||||||
Db       1031 GCCCGCGCCCTGCCC---GCCACCGGCCTGCCCTTCGAGTTCAACCTCGGCTACGTCGGC 1087

Qy        314 TyrLeuGlyTyrGluLeuLysAlaGluThrThrGlyAspProAlaHisArgSerProHis 333
                |||||||||||||||  ||||||::::::  |||:::  |||||||||
Db       1088 TACCTCGGCTACGAGACCAAGGCCGACAGCGGCGGCGAGGACGCCCACCGCGGCGAACTG 1147

Qy        334 ProAspAlaAlaPheLeuPheAlaAspArgAlaIleAlaLeuAspHisGlnGluGlyCys 353
                ||||||  ||||||:::|||||||||||  :::|||||||||||||:::::|||
Db       1148 CCCGACGGCGCCTTCATGTTCGCCGACCGGATGCTCGCCCTCGACCACGAACAGGGGCGG 1207

Qy        354 CysTyrLeuLeuAlaLeuAsp---------ArgArgGlyHisAspAspGlyAlaArgAla 370
                :::|||||||||||||              |||                |||
Db       1208 GCCTGGCTCCTGGCACTGAGCAGCACCCGACGGCCCGCCACCGCACCCGCCGCCGAACGC 1267

Qy        371 TrpLeuArgGluThrAlaGluThrLeuThrGlyLeuAlaValArg--------------- 385
                ||||||  :::  |||  ||||||      |||  |||
Db       1268 TGGCTCACCGACGCCGCCCGGACCCTCGCCACCACCGCCCCCCGCCCGCCCTTCACCCTG 1327

Qy        386 AlaProAlaGluProThrProAlaMetValPheGlyIleProGluAlaAlaAlaGlyPhe 405
                |||   :::      ||||||:::
Db       1328 CTGCCCGACGACCAACTGCCCGCCCTGGAC---------------------------- 1357

Qy        406 GlyProLeuAlaArgAlaArgHisAspLysAspAlaTyrLeuLysArgIleAspGluCys 425
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Db       1358 ---------GTCCACTACCGCCACAGCCTGCCCCGCTACCGGGAACTGGTCGAGGAATGC 1408

Qy        426 LeuLysGluIleArgAsnGlyGluSerTyrGluIleCysLeuThrAsnMetValThrAla 445

Db       1409 CGCCGCCTGATCACCGACGGCGAGACCTACGAGGTGTGCCTGACGAACATGCTCCGGGTG 1468

Qy        446 ProThrGluAlaThrAlaLeuProLeuTyrSerAlaLeuArgAlaIleSerProValPro 465

Db       1469 CCCGGCCGGATCGACCCGCTCACCGCCTACCGCGCCCTGCGCACCGTCAGCCCCGCCCCC 1528

Qy        466 TyrGlyAlaLeuLeuGluProGluLeuSerValLeuSerAlaSerProGluArgPhe 485

Db       1529 TACGCCGCCTACCTGCAGTTCCCCGGGGCCACCGTGCTCAGCTCCTCACCCGAACGGTTC 1588

Qy        486 LeuThrIleGlyAlaAspGlyGlyValGluSerLysProIleLysGlyThrArgProArg 505

Db       1589 CTGCGCATCGGCGCGGACGGTTGGGCGGAGTCCAAACCCATCAAGGGCACCCGCCCCCGC 1648

Qy        506 GlyGlyThrAlaGluGluAspGluArgLeuArgAlaAspLeuAlaGlyArgGluLysAsp 525

Db       1649 GGCGCCGGCCCCGCCCAGGACGCCGCCGTCAAGGCCTCCCTCGCCGCGGCCGAGAAGGAC 1708

Qy        526 ArgAlaGluAsnLeuMetIleValAspLeuValArgAsnAspLeuAsnSerValCysAla 545

Db       1709 CGCAGCGAGAACCTGATGATCGTCGACCTGGTCCGCAACGACCTCGGCCAGGTCTGCGAC 1768

Qy        546 IleGlySerValHisValProArgLeuPheGluValGluThrTyrAlaProValHisGln 565

Db       1769 ATCGGCTCCGTCCACGTACCGGGCCTGTTCGAGGTGGAGACCTACGCCACCGTCCACCAG 1828

Qy        566 LeuValSerThrIleArgGlyArgLeuArgProGlyThrSerThrAlaAlaCysValArg 585

Db       1829 CTCGTCAGCACGGTCCGCGGCCGCCTGGCGGCCGACGTCTCCCGCCCCCGCGCGGTACGG 1888

Qy        586 AlaAlaProGlyGlySerMetThrGlyAlaProLysLysArgThrMetGluIleIle 605

Db       1889 GCCGCCTTCCCCGGCGGGTCGATGACCGGCGCGCCCAAGGTCCGCACCATGCAGTTCATC 1948

Qy        606 AspArgLeuGluGluGlyProArgGlyValTyrSerGlyAlaLeuGlyTrpPheAlaLeu 625

Db       1949 GACCGGCTCGAGAAGGGCCCGCGCGGCGTGTACTCGGGCGCGCTGGGCTACTTCGCCCTC 2008

Qy        626 SerGlyAlaAlaAspLeuSerIleValIleArgThrIleValLeuAlaAspGlyGlnAla 645

Db       2009 AGCGGCGCGGCCGACCTCAGCATCGTCATCCGCACCATCGTCGCCACCGAGGAGGCCGCC 2068

Qy        646 GluPheGlyValGlyGlyAlaIleValSerLeuSerAspGlnGluGluGluPheThrGlu 665

Db       2069 ACCATCGGCGTGGGCGGCGCCGTCGTCGCCCTGTCCGACCCCGACGACGAGGTCCGCGAA 2128

Qy        666 ThrValValLysAlaArgAlaMetValThrAlaLeuAspGlySerAlaValAlaGlyAla 685

Db       2129 ATGCTCCTCAAGGCGCAGACCACCCTCGCCGCCCTG---CGCCAGGCACACGCGGGCGCC 2185
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RESULT 8
STMPABA
LOCUS STMPABA 4607 bp DNA linear BCT 31-AUG-1993
DEFINITION Streptomyces griseus pab gene fragment.
ACCESSION M93058
VERSION M93058.1 GI:153396
KEYWORDS pab gene.
SOURCE Streptomyces griseus
ORGANISM Streptomyces griseus
Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales; Streptomycineae; Streptomycetaceae; Streptomyces.
REFERENCE 1 (bases 1 to 4607)
AUTHORS Criado,L.M., Martin,J.F. and Gil,J.A.
TITLE The pab gene of Streptomyces griseus, encoding p-aminobenzoic acid synthase, is located between genes possibly involved in candicidin biosynthesis
JOURNAL Gene 126 (1), 135-139 (1993)
MEDLINE 93231527
PUBMED 8472954
COMMENT Original source text: Streptomyces griseus (library: IMRU3570) DNA.
FEATURES Location/Qualifiers
source 1. .4607
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CDS 88. .1173
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TGTPRRLRVIAKSLPTRWDAEVAFDSLFRTGDHPFWLDSSRPGGELGQLSMMGDASGP
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LTNMAEADTDLTPWAAYRALRRVSPAPFAAFLDFGPMAVLSSSPERFLRIDRHGRMES
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GEGTETVTEMLERWSGEDPLPVEVRPDSPFLLLPSSGTTSARPKICLHSHEGLLTNSR
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ORIGIN

Alignment Scores:

Pred. No.:	1.6e-77	Length:	4607
Score:	1766.00	Matches:	379
Percent Similarity:	63.88%	Conservative:	72
Best Local Similarity:	53.68%	Mismatches:	211
Query Match:	49.43%	Indels:	44
DB:	1	Gaps:	12

US-10-089-514-2 (1-686) x STMPABA (1-4607)

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Qy          1 MetArgThrLeuLeuIleAspAsnTyrAspSerPheThrHisAsnLeuPheGlnTyrIle 20

Db       1370 ATGCGCACCCTTCTCGTCGACAACTACGACTCGTTCACCTACAACCTCTTCCACTACCTC 1429

Qy         21 GlyGluAlaThrGlyGlnProProValValValProAsn---AspAlaAspTrpSerArg 39
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ORIGIN

Alignment Scores:
Pred. No.:              7.85e-18       Length:          2888
Score:                  256.00         Matches:         51
Percent Similarity:     71.08%         Conservative:    8
Best Local Similarity:  61.45%         Mismatches:      24
Query Match:            49.81%         Indels:          0
DB:                     6              Gaps:            0

US-10-089-514-4 (1-103) x AR198353 (1-2888)

Qy          7 LeuGlnArgLeuArgAlaGluLeuAspAlaLeuAspGlyThrLeuLeuAspThrValArg 26
              |||      |||||||||   ||||||||   |||       ||||||||   |||||
Db       1936 CTCGACGCGCTGCGCGCCCGCCTGGACGCCGCGGACGCCGCCCTGCTGGACGCCGTCCGC 1995

Qy         27 ArgArgIleAspLeuGlyValArgIleAlaArgTyrLysSerArgHisGlyValProMet 46
                 |||:::|||:::   :::||||||        ||||||          |||||||||
Db       1996 ACACGCCTGGACATCTGCCTGCGCATCGGCGAGTACAAGCGCCTCCACCAGGTGCCGATG 2055

Qy         47 MetGlnProGlyArgValSerLeuValLysAspArgAlaAlaArgTyrAlaAlaAspHis 66
              |||||||||   |||::::::   |||      |||||||||||||||||||||||||
Db       2056 ATGCAGCCCCACCGGATCGCCCAGGTCCACGCCAACGCCGCCCGCTACGCCGCCGACCAC 2115

Qy         67 GlyLeuAspGluSerPheLeuValAsnLeuTyrAspValIleIleThrGluMetCysArg 86
              |||:::|||   :::||||||       |||||||||   |||||||||||    ||||||
Db       2116 GGCATCGACCCCGCCTTCCTGCGCACCCTGTACGACACGATCATCACCGAGACCTGCCGC 2175

Qy         87 ValGluAsp 89
               :::||||||
Db       2176 CTCGAGGAC 2184

RESULT 9
SPU60417
LOCUS       SPU60417                4740 bp    DNA     linear   BCT 07-MAR-1997
DEFINITION  Streptomyces pristinaespiralis 4-dimethylamino-L-phenylalanine
            precursor biosynthesis (papA, papC, papB, papM) genes, complete
            cds.
ACCESSION   U60417
VERSION     U60417.1  GI:1575335
KEYWORDS    .
SOURCE      Streptomyces pristinaespiralis
  ORGANISM  Streptomyces pristinaespiralis
            Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;
            Streptomycineae; Streptomycetaceae; Streptomyces.
REFERENCE   1  (bases 1 to 4740)
  AUTHORS   Blanc,V., Gil,P., Bamas-Jacques,N., Lorenzon,S., Zagorec,M.,
            Schleuniger,J., Bisch,D., Blanche,F., Debussche,L., Crouzet,J. and
            Thibaut,D.
  TITLE     Identification and analysis of genes from Streptomyces
            pristinaespiralis encoding enzymes involved in the biosynthesis of
            the 4-dimethylamino-L-phenylalanine precursor of pristinamycin I
  JOURNAL   Mol. Microbiol. 23 (2), 191-202 (1997)
  MEDLINE   97197164
   PUBMED   9044253
REFERENCE   2  (bases 1 to 4740)
  AUTHORS   Blanc,V., Gil,P., Bamas-Jacques,N., Lorenzon,S., Schleuniger,J.,
            Bisch,D., Blanche,F., Debussche,L., Crouzet,J. and Thibaut,D.
  TITLE     Direct Submission
  JOURNAL   Submitted (11-JUN-1996) Recherche Pharmaceutique, Rhone-Poulenc
            Rorer, 13 quai Jules Guesde, B. P. 14, Vitry sur Seine cedex 94403,
            France
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                     RIGADGWAESKPIKGTRPRGAGPAQDAAVKASLAAAEKDRSENLMIVDLVRNDLGQVC
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                     DGCLTAVRNHTCAPPA"
ORIGIN

Alignment Scores:
Pred. No.:              1.33e-17       Length:          4740
Score:                  256.00         Matches:         51
Percent Similarity:     71.08%         Conservative:    8
Best Local Similarity:  61.45%         Mismatches:      24
Query Match:            49.81%         Indels:          0
```

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DB:                    1              Gaps:          0

US-10-089-514-4 (1-103) x SPU60417 (1-4740)

Qy          7 LeuGlnArgLeuArgAlaGluLeuAspAlaLeuAspGlyThrLeuLeuAspThrValArg 26
              |||      |||||||||   |||||||||   |||       ||||||||   ||||||
Db       3476 CTCGACGCGCTGCGCGCCCGCCTGGACGCCGCGGACGCCGCCCTGCTGGACGCCGTCCGC 3535

Qy         27 ArgArgIleAspLeuGlyValArgIleAlaArgTyrLysSerArgHisGlyValProMet 46
                ||:::|||:::   :::||||||      ||||||      |||   |||||||||
Db       3536 ACACGCCTGGACATCTGCCTGCGCATCGGCGAGTACAAGCGCCTCCACCAGGTGCCGATG 3595

Qy         47 MetGlnProGlyArgValSerLeuValLysAspArgAlaAlaArgTyrAlaAlaAspHis 66
              |||||||||   |||::::::   |||                 ||||||||||||||||||
Db       3596 ATGCAGCCCCACCGGATCGCCCAGGTCCACGCCAACGCCGCCCGCTACGCCGCCGACCAC 3655

Qy         67 GlyLeuAspGluSerPheLeuValAsnLeuTyrAspValIleIleThrGluMetCysArg 86
              |||:::|||   :::||||||      |||||||||   ||||||||||||   ||||||
Db       3656 GGCATCGACCCCGCCTTCCTGCGCACCCTGTACGACACGATCATCACCGAGACCTGCCGC 3715

Qy         87 ValGluAsp 89
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Db       3716 CTCGAGGAC 3724

RESULT 10
BX571871/c
LOCUS       BX571871               349944 bp    DNA     linear   BCT 26-SEP-2003
DEFINITION  Photorhabdus luminescens subsp. laumondii TTO1 complete genome;
            segment 13/17.
ACCESSION   BX571871 BX470251
VERSION     BX571871.1  GI:36786846
KEYWORDS    complete genome.
SOURCE      Photorhabdus luminescens subsp. laumondii TTO1
  ORGANISM  Photorhabdus luminescens subsp. laumondii TTO1
            Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales;
            Enterobacteriaceae; Photorhabdus.
REFERENCE   1
  AUTHORS   Duchaud,E., Rusniok,C., Frangeul,L., Buchrieser,C., Taourit,S.,
            Bocs,S., Boursaux-Eude,C., Chandler,M., Dassa,E., Derose,R.,
            Derzelle,S., Freyssinet,G., Gaudriault,S., Givaudan,A., Glaser,P.,
            Medigue,C., Lanois,A., Powell,K., Siguier,P., Wingate,V.,
            Zouine,M., Boemare,N., Danchin,A. and Kunst,F.
  TITLE     Complete genome sequence of the entomopathogenic bacterium
            Photorhabdus luminescens
  JOURNAL   Nat. Biotechnol. 11 (1) (2003) In press
REFERENCE   2
  AUTHORS   Duchaud,E., Frangeul,L., Rusniok,C. and Kunst,F.
  TITLE     Direct Submission
  JOURNAL   Submitted (23-APR-2003) L. Frangeul, Institut Pasteur, Genopole, 25
            rue du Docteur Roux, 75724 Paris Cedex 15, FRANCE. E-mail:
            lfrangeu@pasteur.fr, fkunst@pasteur.fr
FEATURES             Location/Qualifiers
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DEFINITION  Sequence 1 from patent US 6352839.
ACCESSION   AR198353
VERSION     AR198353.1  GI:20248202
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 2888)
  AUTHORS   Blanc,V., Thibaut,D., Bamas-Jacques,N., Blanche,F., Crouzet,J.,
            Barriere,J.-C., Debussche,L., Famechon,A., Paris,J.-M. and
            Dutruc-Rosset,G.
  TITLE     Streptogramins for preparing same by mutasynthesis
  JOURNAL   Patent: US 6352839-A 1 05-MAR-2002;
FEATURES             Location/Qualifiers
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Percent Similarity:       60.38%        Conservative:    34
Best Local Similarity:    49.52%        Mismatches:      101
Query Match:              40.46%        Indels:          23
DB:                       6             Gaps:            4

US-10-089-514-6 (1-322) x AR198353 (1-2888)

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DEFINITION  Streptomyces pristinaespiralis 4-dimethylamino-L-phenylalanine
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            cds.
ACCESSION   U60417
VERSION     U60417.1  GI:1575335
KEYWORDS    .
SOURCE      Streptomyces pristinaespiralis
  ORGANISM  Streptomyces pristinaespiralis
            Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;
            Streptomycineae; Streptomycetaceae; Streptomyces.
REFERENCE   1  (bases 1 to 4740)
  AUTHORS   Blanc,V., Gil,P., Bamas-Jacques,N., Lorenzon,S., Zagorec,M.,
            Schleuniger,J., Bisch,D., Blanche,F., Debussche,L., Crouzet,J. and
            Thibaut,D.
  TITLE     Identification and analysis of genes from Streptomyces
            pristinaespiralis encoding enzymes involved in the biosynthesis of
            the 4-dimethylamino-L-phenylalanine precursor of pristinamycin I
  JOURNAL   Mol. Microbiol. 23 (2), 191-202 (1997)
  MEDLINE   97197164
   PUBMED   9044253
REFERENCE   2  (bases 1 to 4740)
  AUTHORS   Blanc,V., Gil,P., Bamas-Jacques,N., Lorenzon,S., Schleuniger,J.,
            Bisch,D., Blanche,F., Debussche,L., Crouzet,J. and Thibaut,D.
  TITLE     Direct Submission
  JOURNAL   Submitted (11-JUN-1996) Recherche Pharmaceutique, Rhone-Poulenc
            Rorer, 13 quai Jules Guesde, B. P. 14, Vitry sur Seine cedex 94403,
            France
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Alignment Scores:
Pred. No.:              5.79e-20       Length:         4740
Score:                  661.50         Matches:        155
Percent Similarity:     60.38%         Conservative:   34
Best Local Similarity:  49.52%         Mismatches:     101
Query Match:            40.46%         Indels:         23
DB:                     1              Gaps:           4

US-10-089-514-6 (1-322) x SPU60417 (1-4740)

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LOCUS       BX571871               349944 bp    DNA     linear   BCT 26-SEP-2003
DEFINITION  Photorhabdus luminescens subsp. laumondii TTO1 complete genome;
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ACCESSION   BX571871 BX470251
VERSION     BX571871.1  GI:36786846
KEYWORDS    complete genome.
SOURCE      Photorhabdus luminescens subsp. laumondii TTO1
  ORGANISM  Photorhabdus luminescens subsp. laumondii TTO1
            Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales;
            Enterobacteriaceae; Photorhabdus.
REFERENCE   1
  AUTHORS   Duchaud,E., Rusniok,C., Frangeul,L., Buchrieser,C., Taourit,S.,
            Bocs,S., Boursaux-Eude,C., Chandler,M., Dassa,E., Derose,R.,
            Derzelle,S., Freyssinet,G., Gaudriault,S., Givaudan,A., Glaser,P.,
            Medigue,C., Lanois,A., Powell,K., Siguier,P., Wingate,V.,
            Zouine,M., Boemare,N., Danchin,A. and Kunst,F.
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